25.
BÖLÜM

ADRENOKORTİKAL KARSİNOMLARDA ADJUVAN TEDAVİ YAKLAŞIMLARI

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GİRİŞ

Adrenokortikal karsinomlar, fonksiyonel olabilen ve Cushing sendromuna ve / veya virilizasyona neden olabilen veya nonfonksiyonel olup insidental saptanan abdominal kitle olarak görülebilen, sıklığı 1-2/1.000.000 olan, nadir ve çoğunlukla agresif tümörlerdir (1). Kadın ve erkeklerde eşit oranda görülüp, çocukluk çağı ve 40-50 yaş grubunda daha sık rastlanmaktadır (2). %90 sporadik olup, %10 germline mutasyonlar, Li-Fraumeni sendromu, Lynch sendromu, MEN1, ailesel adenomatozis polipozis, Beckwith-Wiedemann, NF1 gibi ailevi kanser sendromlarıyla ilişkili olarak görülmektedir (3). Adrenokortikal karsinom tanısı alan erişkin hastaların Li-Fraumeni ve Lynch sendromları açısından taranması önerilmektedir (4).

EVRELEME VE PROGNOSTİK FAKTÖRLER

Adrenokortikal kanserler için çeşitli evreleme sistemleri mevcuttur. Sağkalımda en önemli prognostik faktörler ise hastalığın evresi ve cerrahi tam rezeksiyondur (5). Bununla birlikte hastalar çoğunlukla ileri evrede saptandıkları için beş yıllık hastalıksız sağkalım oranları oldukça düşüktür. Evre I, II, III ve IV (metastatik) hastalık için beş yıllık genel sağkalım oranları sırasıyla yüzde 66, 58, 24 ve 0 olarak bildirilmiştir (6).

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klinik ve biyokimyasal belirtileri ortaya çıktığında, fludrokortizon (günlük 0.1 ila 0.3 mg) replasmanı yapılmalıdır.

- Sitotoksik kemoterapinin tek başına veya mitotan ile kombinasyon halinde tek başına adjuvan mitotana göre daha etkili olup olmadığı bilinmemektedir. Yine de erken rekürrens için yüksek risk altında olduğu düşünülen hastalarda sisplatin bazlı bir adjuvan rejim düşünülebilir.
- Adjuvan RT'nin yararı, lokal kontrol ile sınırlıdır. R1 veya Rx rezeksiyonlu hastalarda, evre III hastalığı olanlarda, rezeksiyon sırasında tümör dağılması olan ve yüksek dereceli AKK (Ki 67> %10 veya 50 HPF > 20 mitotik figür) olan hastalarda ideal olarak postoperatif 12 hafta içinde RT başlanması önerilmektedir.

KAYNAKLAR

1. Ng L, Libertino JM. Adrenocortical carcinoma: diagnosis, evaluation and treatment. J Urol 2003; 169:5.
2. Hsing AW, Nam JM, Co Chien HT, et al. Risk factors for adrenal cancer: an exploratory study. Int J Cancer 1996; 65:432.
3. Sandrini R, Ribeiro RC, DeLacerda L. Childhood adrenocortical tumors. J Clin Endocrinol Metab 1997; 82:2027.
4. Allolio B, Fassnacht M. Clinical review: Adrenocortical carcinoma: clinical update. J Clin Endocrinol Metab 2006; 91:2027.
5. Fassnacht M, Dekkers O, Else T, et al. European Society of Endocrinology Clinical Practice Guidelines on the Management of Adrenocortical Carcinoma in Adults, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 2018.
6. Icard P, Goudet P, Charpenay C, et al. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. World J Surg 2001; 25:891.
7. Weiss LM, Medeiros LJ, Vickery AL Jr. Pathologic features of prognostic significance in adrenocortical carcinoma. Am J Surg Pathol 1989; 13:202.
8. Beuschlein F, Weigel J, Saeger W, et al. Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. J Clin Endocrinol Metab 2015; 100:841.
9. Abiven G, Coste J, Groussin L, et al. Clinical and biological features in the prognosis of adrenocortical cancer: poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients. J Clin Endocrinol Metab 2006; 91:2650.

10. Stojadinovic A, Ghossein RA, Hoos A, et al. Adrenocortical carcinoma: clinical, morphologic, and molecular characterization. J Clin Oncol 2002; 20:941.
11. de Reyniès A, Assié G, Rickman DS, et al. Gene expression profiling reveals a new classification of adrenocortical tumors and identifies molecular predictors of malignancy and survival. J Clin Oncol 2009; 27:1108.
12. Zheng S, Cherniack AD, Dewal N, et al. Comprehensive Pan-Genomic Characterization of Adrenocortical Carcinoma. Cancer Cell 2016; 29:723.
13. Icard P, Goudet P, Charpenay C, et al. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. World J Surg 2001; 25:891.
14. Vassilopoulou-Sellin R, Schultz PN. Adrenocortical carcinoma. Clinical outcome at the end of the 20th century. Cancer 2001; 92:1113.
15. Raj N, Zheng Y, Kelly V, et al. PD-1 Blockade in Advanced Adrenocortical Carcinoma. J Clin Oncol 2020; 38:71.
16. abra MA, Stephen B, Campbell M, et al. Phase II clinical trial of pembrolizumab efficacy and safety in advanced adrenocortical carcinoma. J Immunother Cancer 2019; 7:253.
17. Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020; 21:121.
18. Miller BS, Gauger PG, Hammer GD, et al. Proposal for modification of the ENSAT staging system for adrenocortical carcinoma using tumor grade. Langenbecks Arch Surg 2010; 395:955.
19. Giordano TJ. The argument for mitotic rate-based grading for the prognostication of adrenocortical carcinoma. Am J Surg Pathol 2011; 35:471.
20. Bertagna C, Orth DN. Clinical and laboratory findings and results of therapy in 58 patients with adrenocortical tumors admitted to a single medical center (1951 to 1978). Am J Med 1981; 71:855.
21. Henley DJ, van Heerden JA, Grant CS, et al. Adrenal cortical carcinoma--a continuing challenge. Surgery 1983; 94:926.
22. Hutter AM Jr, Kayhoe DE. Adrenal cortical carcinoma. Clinical features of 138 patients. Am J Med 1966; 41:572.
23. Nader S, Hickey RC, Sellin RV, Samaan NA. Adrenal cortical carcinoma. A study of 77 cases. Cancer 1983; 52:707.
24. Schteingart DE, Doherty GM, Gauger PG, et al. Management of patients with adrenal cancer: recommendations of an international consensus conference. Endocr Relat Cancer 2005; 12:667.
25. Schteingart DE, Motazedi A, Noonan RA, Thompson NW. Treatment of adrenal carcinomas. Arch Surg 1982; 117:1142.
26. Khorram-Manesh A, Ahlman H, Jansson S, et al. Adrenocortical carcinoma: surgery and mitotane for treatment and steroid profiles for follow-up. World J Surg 1998; 22:605.

27. Crucitti F, Bellantone R, Ferrante A, et al. The Italian Registry for Adrenal Cortical Carcinoma: analysis of a multiinstitutional series of 129 patients. The ACC Italian Registry Study Group. Surgery 1996; 119:161.
28. Luton JP, Cerdas S, Billaud L, et al. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. N Engl J Med 1990; 322:1195.
29. Wajchenberg BL, Albergaria Pereira MA, Medonca BB, et al. Adrenocortical carcinoma: clinical and laboratory observations. Cancer 2000; 88:711.
30. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med 2007; 356:2372.
31. Schteingart DE. Adjuvant mitotane therapy of adrenal cancer - use and controversy. N Engl J Med 2007; 356:2415.
32. Berruti A, Grisanti S, Pulzer A, et al. Long-Term Outcomes of Adjuvant Mitotane Therapy in Patients With Radically Resected Adrenocortical Carcinoma. J Clin Endocrinol Metab 2017; 102:1358.
33. Fassnacht M, Johanssen S, Fenske W, et al. Improved survival in patients with stage II adrenocortical carcinoma followed up prospectively by specialized centers. J Clin Endocrinol Metab 2010; 95:4925.
34. Else T, Williams AR, Sabolch A, et al. Adjuvant therapies and patient and tumor characteristics associated with survival of adult patients with adrenocortical carcinoma. J Clin Endocrinol Metab 2014; 99:455.
35. Calabrese A, Basile V, Puglisi S, et al. Adjuvant mitotane therapy is beneficial in non-metastatic adrenocortical carcinoma at high risk of recurrence. Eur J Endocrinol 2019; 180:387.
36. Pommier RF, Brennan MF. An eleven-year experience with adrenocortical carcinoma. Surgery 1992; 112:963.
37. Volante M, Bollito E, Sperone P, et al. Clinicopathological study of a series of 92 adrenocortical carcinomas: from a proposal of simplified diagnostic algorithm to prognostic stratification. Histopathology 2009; 55:535.
38. Berruti A, Fassnacht M, Baudin E, et al. Adjuvant therapy in patients with adrenocortical carcinoma: a position of an international panel. J Clin Oncol 2010; 28:e401.
39. Fassnacht M, Libé R, Kroiss M, Allolio B. Adrenocortical carcinoma: a clinician's update. Nat Rev Endocrinol 2011; 7:323.
40. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. https://www.nccn.org/professionals/physician_gls (Accessed on May 06, 2021).
41. de Reyniès A, Assié G, Rickman DS, et al. Gene expression profiling reveals a new classification of adrenocortical tumors and identifies molecular predictors of malignancy and survival. J Clin Oncol 2009; 27:1108.
42. Zheng S, Cherniack AD, Dewal N, et al. Comprehensive Pan-Genomic Characterization of Adrenocortical Carcinoma. Cancer Cell 2016; 29:723.
43. assnacht M, Allolio B. What is the best approach to an apparently nonmetastatic adrenocortical carcinoma? Clin Endocrinol (Oxf) 2010; 73:561.

44. Haak HR, Hermans J, van de Velde CJ, et al. Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. Br J Cancer 1994; 69:947.
45. van Slooten H, Moolenaar AJ, van Seters AP, Smeenk D. The treatment of adrenocortical carcinoma with o,p'-DDD: prognostic implications of serum level monitoring. Eur J Cancer Clin Oncol 1984; 20:47.
46. Mauclère-Denost S, Leboulleux S, Borget I, et al. High-dose mitotane strategy in adrenocortical carcinoma: prospective analysis of plasma mitotane measurement during the first 3 months of follow-up. Eur J Endocrinol 2012; 166:261.
47. Ronchi CL, Sbiera S, Volante M, et al. CYP2W1 is highly expressed in adrenal glands and is positively associated with the response to mitotane in adrenocortical carcinoma. PLoS One 2014; 9:e105855.
48. D'Avolio A, De Francia S, Basile V, et al. Influence of the CYP2B6 polymorphism on the pharmacokinetics of mitotane. Pharmacogenet Genomics 2013; 23:293.
49. Kerkhofs TM, Derijks LJ, Ettaieb MH, et al. Short-term variation in plasma mitotane levels confirms the importance of trough level monitoring. Eur J Endocrinol 2014; 171:677.
50. Zini L, Porpiglia F, Fassnacht M. Contemporary management of adrenocortical carcinoma. Eur Urol 2011; 60:1055.
51. Deandreis D, Leboulleux S, Caramella C, et al. FDG PET in the management of patients with adrenal masses and adrenocortical carcinoma. Horm Cancer 2011; 2:354.
52. van Seters AP, Moolenaar AJ. Mitotane increases the blood levels of hormone-binding proteins. Acta Endocrinol (Copenh) 1991; 124:526.
53. De León DD, Lange BJ, Walterhouse D, Moshang T. Long-term (15 years) outcome in an infant with metastatic adrenocortical carcinoma. J Clin Endocrinol Metab 2002; 87:4452.
54. Robinson BG, Hales IB, Henniker AJ, et al. The effect of o,p'-DDD on adrenal steroid replacement therapy requirements. Clin Endocrinol (Oxf) 1987; 27:437.
55. Chortis V, Taylor AE, Schneider P, et al. Mitotane therapy in adrenocortical cancer induces CYP3A4 and inhibits 5α-reductase, explaining the need for personalized glucocorticoid and androgen replacement. J Clin Endocrinol Metab 2013; 98:161.
56. Manenschijn L, Quinkler M, van Rossum EF. Hair cortisol measurement in mitotane-treated adrenocortical cancer patients. Horm Metab Res 2014; 46:299.
57. Daffara F, De Francia S, Reimondo G, et al. Prospective evaluation of mitotane toxicity in adrenocortical cancer patients treated adjuvantly. Endocr Relat Cancer 2008; 15:1043.
58. Salenave S, Bernard V, Do Cao C, et al. Ovarian macrocysts and gonadotrope-ovarian axis disruption in premenopausal women receiving mitotane for adrenocortical carcinoma or Cushing's disease. Eur J Endocrinol 2015; 172:141.
59. Else T, Kim AC, Sabolch A, et al. Adrenocortical carcinoma. Endocr Rev 2014; 35:282.
60. Kroiss M, Quinkler M, Lutz WK, et al. Drug interactions with mitotane by induction of CYP3A4 metabolism in the clinical management of adrenocortical carcinoma. Clin Endocrinol (Oxf) 2011; 75:585.

61. van Erp NP, Guchelaar HJ, Ploeger BA, et al. Mitotane has a strong and a durable inducing effect on CYP3A4 activity. Eur J Endocrinol 2011; 164:621.
62. Fassnacht M, Kroiss M, Allolio B. Update in adrenocortical carcinoma. J Clin Endocrinol Metab 2013; 98:4551.
63. Hovi L, Wikström S, Vettenranta K, et al. Adrenocortical carcinoma in children: a role for etoposide and cisplatin adjuvant therapy? Preliminary report. Med Pediatr Oncol 2003; 40:324.
64. Khan TS, Imam H, Juhlin C, et al. Streptozocin and o,p'DDD in the treatment of adrenocortical cancer patients: long-term survival in its adjuvant use. Ann Oncol 2000; 11:1281.
65. Polat B, Fassnacht M, Pfreundner L, et al. Radiotherapy in adrenocortical carcinoma. Cancer 2009; 115:2816.
66. Fassnacht M, Hahner S, Polat B, et al. Efficacy of adjuvant radiotherapy of the tumor bed on local recurrence of adrenocortical carcinoma. J Clin Endocrinol Metab 2006; 91:4501.
67. Markoe AM, Serber W, Micaily B, Brady LW. Radiation therapy for adjunctive treatment of adrenal cortical carcinoma. Am J Clin Oncol 1991; 14:170.
68. Sabolch A, Else T, Griffith KA, et al. Adjuvant radiation therapy improves local control after surgical resection in patients with localized adrenocortical carcinoma. Int J Radiat Oncol Biol Phys 2015; 92:252.
69. Nelson DW, Chang SC, Bandera BC, et al. Adjuvant Radiation is Associated with Improved Survival for Select Patients with Non-metastatic Adrenocortical Carcinoma. Ann Surg Oncol 2018; 25:2060.
70. Viani GA, Viana BS. Adjuvant radiotherapy after surgical resection for adrenocortical carcinoma: A systematic review of observational studies and meta-analysis. J Cancer Res Ther 2019; 15:S20.